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Exploring Indications for the Use of Direct Oral Anticoagulants and the Associated Risks of Major Bleeding

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Abstract

Thrombosis is a leading cause of morbidity and mortality in the United States. Arterial and venous thromboses are implicated in the pathogenesis of major disorders, including myocardial infarction, ischemic stroke, and venous thromboembolism. Over the past decade, direct oral anticoagulants (DOACs) (eg, direct thrombin inhibitor and factor Xa [FXa] inhibitors) have been adopted as alternatives to warfarin due to their clinical advantages and efficacy for the treatment of thrombosis. As with all anticoagulants, treatment with DOACs is associated with a risk of major bleeding, including life-threatening gastrointestinal bleeds and intracranial hemorrhages (ICHs). In turn, the burden of bleeding associated with DOAC treatment is itself associated with substantial healthcare costs that are amplified by an increased risk of thromboembolic events and mortality following major bleeding events, especially in patients with ICHs. Given the rapid adoption of the DOACs and projected usage in the large patient population affected by thromboembolic conditions, clinicians are increasingly likely to encounter patients with major bleeding events due to DOAC therapy. Unlike warfarin, effective strategies to manage these bleeds are limited. There is an unmet need for reversal agents for use in the management of patients who receive FXa inhibitors and experience life-threatening bleeding or need emergency surgery. Andexanet alfa and ciraparantag are being evaluated as potential antidotes for both direct and indirect FXa inhibitors.

"If given a choice between bleeding and thrombosis, treat bleeding. **It's easier.**"

—*Anonymous hematologic axiom*

Expert Opinion

As part of the physiological aging process, the human body experience age-related changes in the hemostatic system that ca lead to an imbalance between the 2 extremes of bleeding

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and thrombosis. These changes result in a heightened procoagulant state and enhanced risk for thromboembolic conditions. In 1856, Virchow described the mechanisms underlying thrombosis as involving a pathologic triad of stasis, endothelial cell injury, and hypercoagulability.[1] Both arterial and venous thromboses are implicated in the pathogenesis of major disorders that include ischemic stroke and venous thromboembolism (VTE, including deep vein thrombosis [DVT] and pulmonary embolism [PE]).[2] Thrombosis is a leading cause of morbidity and mortality in the United States and worldwide.[3–6]

For more than 50 years, oral anticoagulant therapy with warfarin has been used for the treatment and prevention of VTE and for the prophylaxis of stroke in patients with atrial fibrillation (AF). This vitamin K antagonist (VKA), or coumarin class anticoagulant, was first discovered in spoiled sweet clover ingested by Wisconsin cows and then used as a rodenticide. Warfarin was subsequently synthesized and tested in humans starting in the 1950s.[7] Although VKAs proved to be very effective drugs, reducing the risk of stroke in patients with AF by two-thirds, they are associated with several clinical limitations.[8] Treatment with coumarins requires frequent blood testing (eg, prothrombin time and international normalized ratio [INR]). Warfarin dosage adjustments are needed to maintain patients within the therapeutic INR range.[7,9] Medication noncompliance and genetic variations in coumarin metabolism can lead to difficulties in achieving and maintaining therapeutic INR levels. Furthermore, coumarins are associated with multiple drug interactions and dietary restrictions, and alcohol consumption may interfere with warfarin metabolism and availability.[10–13]

Over the past decade, direct oral anticoagulants (DOACs) have been adopted as alternatives to VKAs because they are more convenient (ie, no requirement for routine blood tests) and maintain their effectiveness in thrombosis reduction.[14,15] These novel compounds were discovered through research involving organisms that produce anticoagulants. A factor Xa (FXa) inhibitor was isolated from tick saliva and the first thrombin inhibitor, or inhibitor of factor IIa (FIIa), was isolated from leeches.[16] The development of oral forms of these 2 drug classes launched a revolution in anticoagulation. Several clinical trials and meta-analyses showed the DOACs were clinically advantageous and at least as effective as warfarin, the primary VKA used in the United States.[9,17–20] The proven efficacy of DOACs led to FDA approval of the direct thrombin inhibitor dabigatran (Pradaxa) and the FXa inhibitors rivaroxaban (Xarelto), apixaban (Eliquis) and edoxaban (Savaysa) for the treatment and prevention of thromboembolic events (Table 1[21–26]).[21–24] An additional DOAC (betrixaban) is currently in development.[25,26]

Compared with warfarin, DOACs are associated with a reduction in the occurrence of intracranial hemorrhage (ICH), a life-threatening complication of anticoagulant therapy.[8,19,20,27] In addition, DOACs have the potential to help address an unmet clinical need among patients at risk for thromboembolic events: to advance the quality of anticoagulation therapy by offering an alternative to warfarin. Warfarin is underused, as the risk of thrombosis is often underestimated and treatment is inconvenient. Studies have shown that anticoagulant treatment is used in less than half of patients at risk for thromboembolic events (who have risk stratification scores indicating a need for anticoagulation).[28–31]

Due to their ease of clinical use, DOACs are increasingly being prescribed instead of warfarin.[20,32,33] However, as with all anticoagulants, DOACs are associated with a risk of life-threatening bleeding. Given their rapid adoption and their projected usage within the large patient population affected by thromboembolic conditions, clinicians are increasingly likely to encounter patients with major bleeding events due to DOAC therapy.[20,33] And unlike warfarin, there is no approved reversal agent for FXa inhibitors.[34] Thus, there is an unmet need for reversal agents to these anticoagulants for the management of life-threatening bleeding or in the case of emergency surgery.[20]

In this review, we summarize the burden of thrombosis in terms of stroke and VTE and highlight indications for DOAC treatment of these conditions. We also discuss the DOAC-associated bleeding burden and unmet needs for furthering this field of medicine.

Burden of Thrombosis

Venous Thromboembolism/Deep Vein Thrombosis and Pulmonary Embolism

VTE can be manifested as DVT, PE, or both. DVT most commonly presents in the lower extremities, although it can also affect the upper extremities. A PE is a potentially fatal VTE manifestation that results from thrombus embolization and subsequent migration to the lungs.[6] VTE poses a substantial burden on healthcare systems worldwide, as it is associated with substantial morbidity and mortality and is the leading cause of preventable hospital death.[3–6] Although the exact number of patients affected by VTE is unknown, in the United States, the CDC has estimated that between 350,000 and 900,000 people develop blood clots for the first time each year,[35] numbers that exceed the estimated new cases for each of the top 10 cancers in 2016.[36] In the United States alone, 60,000 to 180,000 deaths are directly or indirectly a result of DVT or PE. Modeling data suggest that as many as 300,000 VTE-related deaths may occur every year.[3,4,35,37] In Europe, however, there are approximately 544,000 VTE-related deaths every year.[38] The 30-day mortality rate among patients with VTE in the United States has been estimated at 10% to 30%, and sudden death occurs in 20% to 25% of patients with PE.[6]

In the United States, 7.7 million to 8 million patients are at risk for developing VTE.[28,39] Older patients and those who have been hospitalized are at an especially high risk.[6,28] Worldwide, there are approximately 10 million cases of hospital-associated VTE every year, and up to 60% of these cases occur during or after hospitalization.[2,3,40] In the United States, up to half of outpatient VTE occurrences can be linked to hospitalization, and the risk among hospitalized patients extends for at least 30 days and up to 3 months post discharge.[6,41] Patients with VTE are also at increased risk of recurrence and comorbidities, including chronic thromboembolic pulmonary hypertension, postthrombotic syndrome, and complications of chronic venous insufficiency.[6]

VTE represents a substantial burden on the healthcare system in the United States: estimated annual healthcare costs for incident and recurrent cases of DVT or PE range from $7594 to $16,644 per patient.[6] Given variations in the total projected VTE cases each year, approximations of expenditures in the United States related to VTE range from $2 billion to $10 billion annually.[6] Healthcare systems have the potential to reduce the clinical and

economic burden associated with VTE by assessing a patient's risk of thrombosis at the time of hospital admission and initiating antithrombotic therapy as appropriate.

Ischemic Stroke

In developed nations, ischemic stroke accounts for up to 85% of stroke incidence and approximately 15% to 30% of ischemic strokes are cardioembolic in origin.[3,42] Additionally, up to 30% of cryptogenic ischemic strokes may be due to an occult cardiac source.[42] AF is associated with an increase in the risk of ischemic stroke by a factor of 4 to 5, and cardiac embolism related to AF accounts for up to 15% of strokes in persons of all ages and 30% in persons older than 80 years.[18] The aging population is at a higher risk of developing AF, which may lead to ischemic stroke. The risk of AF increases from 0.1% in adults younger than 55 years to 9% in adults 80 years and older.[3] In 2008, the incidence of ischemic stroke was 545 per 100,000 in the Medicare population in the United States.[3]

Anticoagulant Therapy for Patients With VTE and Patients With AF

Anticoagulant therapy with warfarin and DOACs is approved for patients at risk of thromboembolic complications, such as ischemic stroke, and for prophylaxis and treatment of DVT and PE.[10,14] Treating at-risk patients with appropriate anticoagulant therapy may reduce the incidence and frequency of hospital readmissions and thrombosis-related morbidity and mortality.[3] In the United States, less than half (48%) of at-risk hospitalized medical patients receive VTE prophylaxis as recommended by evidence-based guidelines, despite the availability of oral and nonoral anticoagulants (eg, low-molecular weight heparin, unfractionated heparin, fondaparinux).[28,29] Among patients with nonvalvular AF, 41.3% who require stroke prophylaxis (by $CHADS_2$ [congestive heart failure, hypertension, age, diabetes, stroke (doubled)] stroke risk score) are treated with anticoagulants. This treatment gap leads to approximately 200,000 unnecessary strokes each year in the United States.[31]

The mechanisms of action of various anticoagulants are shown in Figure 1[10,21–25,43]. Warfarin inhibits vitamin K epoxide reductase, thereby reducing the level of clotting factors II, VII, IX, and X, and proteins C and S.[10] In contrast, DOACs specifically target amplification steps in the coagulation cascade by inhibiting FXa or FIIa.[21–24]

DOACs: Advantages Compared With Warfarin

DOACs have predictable dose-dependent pharmacokinetics and pharmacodynamics and fixed dosing; routine monitoring of their anticoagulant activity is not required.[8,19,44,45] Unlike warfarin, DOACs have limited drug interactions and no food interactions. They also have a shorter half-life compared with VKAs and thus a relatively quick onset of anticoagulant activity.[8,19,27,45]

DOACs: Disadvantages Compared With Warfarin

Lack of Reversal Agent—For patients treated with warfarin, effective reversal agents are available for use (either prothrombin complex concentrates [PCCs] or fresh frozen plasma along with vitamin K).[46] A reversal agent (idarucizumab) is also available for dabigatran, a

thrombin inhibitor[47,48]; however, there is no reversal agent currently approved for direct oral FXa inhibitors.[46] Reversal agents could be needed in many of the approximately 84,000 cases of oral FXa inhibitor-associated bleeding observed each year,[49] a number that is likely to go up. Fueling this growth are the aging of the population (as the risk for thromboembolic conditions increases with age) and the increasing frequency of DOAC use; as the number of patients who are prescribed FXa inhibitors increases, so will the number of patients who need reversal agents.[20,33,50]

Current strategies to manage life-threatening bleeding in patients receiving oral FXa inhibitors and options for emergent anticoagulation reversal for invasive procedures are limited and will be described in more detail later in this article. Although DOACs may be associated with lower risks of ICH and major hemorrhage compared with warfarin, the inability to reverse these agents may cause providers to be hesitant to prescribe them, particularly in patients at higher risk of bleeding (eg, patients with higher HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly] bleeding risk scores).[31]

Lack of Laboratory Assay for DOAC Activity—Although patients treated with DOACs do not require routine coagulation monitoring, evaluation of anticoagulant activity may be desirable in certain clinical situations.[51] For example, knowledge of whether the patient is in an appropriate therapeutic range may be useful when treating patients who cannot provide an accurate history of DOAC use, with suspected noncompliance, and with hepatic or renal insufficiency.[52] Similarly, in situations where the degree of drug exposure is unknown and urgent reversal is required, fast and accurate laboratory indicators of coagulation status may be needed.[51] Laboratory measures of coagulopathy may also be useful for selecting DOAC dosing regimens, particularly in obese patients for whom optimal dosing is not currently known.[51]

Chromogenic drug assays are available for dabigatran, apixaban, and rivaroxaban; however, these assays are performed only at select institutions or as part of clinical trials and the results are frequently not available within a clinically meaningful timeframe. Gold standard coagulation studies (ie, dilute thrombin time and ecarin clotting time for dabigatran; drug-specific chromogenic anti-FXa activity for direct oral FXa inhibitors) are expensive and not currently available at most institutions.[51,52]

Drug Cost—When evaluating patient out-of-pocket drug costs, warfarin is a less expensive treatment compared with DOACs. However, this does not factor in the costs of laboratory tests and office visits associated with warfarin titration. Additionally, DOAC treatment is more effective at preventing thrombosis-related clinical events and thereby reduces overall healthcare costs. Multiple cost-effectiveness studies have favored DOACs relative to treatment with warfarin, although this benefit with DOACs for stroke prevention in nonvalvular AF may be smaller compared with quality warfarin anticoagulation management (ie, longer time spent within the recommended therapeutic INR range of 2–3).[53–59]

Rapid Adoption of DOACs

Physicians have been quick to employ DOACs in clinical practice; for example, DOACs are replacing warfarin for the treatment of VTE or stroke and systemic embolism prevention among patients with AF (Figure 2[33]).[32,33] An analysis of commercial and Medicare databases revealed that an estimated 2.9 million patients were treated with a direct FXa inhibitor in the United States in 2015.[49] Although warfarin dominated the anticoagulant market from early 2014 through the end of 2015, dispensed prescriptions for rivaroxaban, apixaban, and edoxaban rose 73.6% and warfarin prescriptions decreased by 10.9%.[32]

As the risk for thromboembolic conditions increases with age, and as the population ages in the United States, the use of FXa inhibitors will become more prevalent. Given the rapid adoption of DOACs and their projected usage increase in the large patient population affected by thromboembolic conditions, clinicians are increasingly likely to encounter patients who are receiving treatment with these anticoagulants and must be prepared to address bleeding.[20,50]

Risk of Bleeding Associated With DOACs

Epidemiology of Bleeding

DOACs have demonstrated efficacy in VTE treatment and stroke prevention; however, their treatment is associated with a risk of bleeding, including life-threatening gastrointestinal (GI) bleeds and ICHs. Data from clinical trials and real-world analyses have consistently shown major bleeding in approximately 3% to 4% of DOAC-treated patients.[9,60,61]

Based on an analysis of data from the Dresden registry and the registry of the Department of Defense of the United States, the rates of major bleeding ranged from 2.9% to 3.4% per year with rivaroxaban treatment.[60,61] In addition, in clinical trials of patients with AF receiving DOAC treatment, 1.6% to 3.6% of patients experienced major bleeding per year[8,18,19,27,62] and trials investigating the efficacy of DOACs as VTE prophylaxis and treatment reported major bleeding rates ranging from 0.47% to 1.6%.[44,63–70] In clinical trials of patients treated with DOACs, ICHs accounted for approximately 13% of major bleeds in DOAC-treated patients, with rates ranging from 8% to 16%, and GI bleeds accounted for up to 56% of all major bleeding events (Figure 3[8,18,19,27,44,62–67,71]).[8,18,19,27,44,62–67,71]

An analysis of data from the Marketscan Commercial and Medicare database from January 1, 2011, to December 31, 2014, showed that of approximately 93,000 patients with AF treated with FXa inhibitors, approximately 3100 patients (3.3%) were hospitalized for DOAC-associated major bleeding events. GI bleeding was the predominant type of bleed, at 57.6%, whereas ICHs represented 9.1% of total bleeds.[49,72] A total of 85.8% of patients hospitalized for major bleeding were treated with rivaroxaban and 14.3% received apixaban.[72] The hospitalization and bleeding rates associated with rivaroxaban and apixaban may have been influenced by the dates of FDA approval of these drugs. Rivaroxaban (2011) received FDA approval prior to apixaban (2012) and thus had a head start in terms of clinical use.[22,23]

Another analysis of data from the Marketscan Commercial and Medicare database showed that of the 2.9 million patients treated with FXa inhibitors in 2015, approximately 84,000 patients (2.9%) had bleeding-related inpatient admissions.[49] Given the rate of major bleeds that are ICHs (13%), this admission rate suggests that more than 900 ICHs associated with FXa inhibitors occur each month in the United States. Notably, though, based on the results of randomized controlled trials, the rates of major bleeding and ICHs with DOACs are similar, even significantly lower in some cases compared with warfarin (Table 2[8,18,19,27,44,63–70,73,74]).[8,18,19,27,44,63–70,73,74] However, secondary outcome results of these randomized trials suggest that certain DOACs (including rivaroxaban, high-dose dabigatran, and high-dose edoxaban) may be associated with a higher risk of GI bleeding compared with warfarin.[18,27,74]

Mortality and Complications Associated With Major Bleeding

Major bleeding events are associated with an increased risk of mortality, and 30-day mortality rates after major bleeding are especially high for patients with ICHs—up to 45% (Figure 4A[75]).[75] In a meta-analysis of 10 clinical trials involving the use of DOACs for the treatment of VTE (manifested as DVT or severe PE), an adjusted case fatality rate of major bleeding events was observed among patients receiving DOAC treatment compared with 10% among patients receiving standard treatment. Of all DOAC-related major bleeds, ICHs accounted for 11% and was associated with a 4-fold increased risk of mortality compared with extracranial major bleeds.[62]

Across 3 pivotal controlled clinical trials of DOACs for the prevention of stroke in patients with AF, the mortality rates due to major bleeding events among patients with AF ranged from 0.30% to 0.38%.[8,18,27] In the ARISTOTLE trial, 0.57% of patients treated with apixaban experienced an ICH event and 1.16% of patients had major GI bleeding.[8] Among patients with non-ICH major bleeding, 8.9% treated with apixaban and 9.5% treated with warfarin died within 30 days of the bleeding event. This corresponded to a 12-fold elevation in the risk of death or thromboembolic event during the 30 days following major non-ICH bleeding. The risk of 30-day mortality was substantially higher in patients with ICHs, as 45.3% of patients treated with apixaban who experienced an ICH died within 30 days of the bleeding event.[75]

In the ENGAGE AF-TIMI 48 study, an ICH occurred in 0.39% of patients who received high-dose edoxaban and in 0.26% of patients treated with low-dose edoxaban. Fatal ICH events occurred in 0.15% and 0.08% of patients treated with high-dose and low-dose edoxaban, respectively. The annual rate of GI bleeds was 1.51% in patients treated with high-dose edoxaban compared with 0.82% in patients treated with low-dose edoxaban.[27]

In the ROCKET AF trial, 0.8% of rivaroxaban-treated patients had an ICH (defined as any primary bleed into the cranial cavity). Events of major bleeding in a GI site occurred in 3.2% of patients treated with rivaroxaban.[18] Among patients with ICHs, 43% did not survive the first 30 days after the event; at 90 days, roughly half (49%) had died.[76]

In a retrospective chart review study, data were collected from patients treated with an FXa inhibitor and admitted with a serious life-threatening acute major bleeding event between

January 2014 and April 2016 across 5 medical centers.[77,78] Among 56 patients, the overall mortality rate at 30 days after discharge was 21.4%. For patients admitted with ICH (n = 19), the mortality rate at 30 days was 36.8%.[77] For patients admitted with GI bleeding (n = 29), the mortality rate 30 days after discharge was 13.8%.[78]

Patients who experience a major bleed are also at higher risk of developing subsequent thromboembolic events.[60,75,79,80] The results of an ancillary study of the ARISTOTLE trial showed a marked increase in the 30-day risk of thromboembolic events (ischemic stroke or myocardial infarction [MI]) following a major bleed in patients taking apixaban or warfarin (Figure 4B[75]).[75] An analysis of trial data from the ROCKET AF trial revealed a rate of thromboembolic events (stroke, systemic embolism, MI, unstable angina) of 7.2% following major bleeds in patients taking rivaroxaban (Figure 4C[60,71,81]).[71] A review of data from the Dresden registry showed that 5 patients taking rivaroxaban experienced thromboembolic events (ischemic stroke, cardiac death, MI, and ischemic attack) within 35 days of a major bleed (Figure 4C[60,71,81]).[60] Analysis of data from a different registry revealed a VTE event rate of 12% within 30 days of a DOAC-associated major bleed (Figure 4C[60,71,81]).[81] These studies did not report whether recurrent thromboembolic events occurred on or off anticoagulation.

Burden of Bleeding

The retrospective chart review study evaluated the burden of disease and resource utilization associated with current strategies for the management of major bleeding.[77,78] Among 56 patients treated with an FXa inhibitor and admitted with major bleeding, 24 (43%) received various factor or plasma products and the remainder received supportive care.[77,78] The use of healthcare resources was substantial, with patients primarily admitted to intensive inpatient settings and seeing a median of 4 physician specialists. No significant differences in resource utilizations and outcomes were observed between patients receiving factor or plasma products versus supportive care.

An analysis of data from the Marketscan Commercial and Medicare database from January 1, 2011, to December 31, 2014, offered insight into the burden of healthcare costs associated with major bleeding in patients with AF.[72,49] Among all hospitalizations for major bleeding events, independent of bleed location, the average patient hospitalization stay lasted 10 days and the mean total healthcare costs for patients with major bleeding was estimated at $58,169. In contrast, the mean hospital payments for ICHs and GI bleeds were $45,447 and $19,819, respectively.[72] Total all-cause healthcare costs were higher during the 12 months of follow-up for patients with AF with major bleeding compared with patients without major bleeding ($63,866 vs $37,916; $P < .001$).[72,49]

These retrospective analyses show that the burden of bleeding associated with DOAC treatment is substantial and that there is an unmet need for reversal agents for use in the management of patients who receive FXa inhibitors and experience life-threatening bleeding or need emergency surgery.[20]

Management of Major Bleeding Associated with DOACs

Current Management Strategies

Specific treatment options are needed for patients taking a DOAC who experience major bleeding. Idarucizumab is a humanized monoclonal antibody indicated for reversal of the anticoagulant effects of dabigatran.[47] Among 494 patients with dabigatran-related life threatening or uncontrolled bleeding or those who required urgent procedures, idarucizumab successfully reversed the anticoagulant effect of dabigatran within the first 4 hours (median) after administration.[48,82] There are no specific reversal products currently available for the direct oral FXa inhibitors.

Current treatment strategies for patients with life-threatening bleeding associated with oral FXa inhibitors include PCCs or activated prothrombin complex concentrates (aPCC; factor VIII inhibitor bypassing activity [FEIBA]). However, PCCs and aPCCs are potentially prothrombotic agents, are not specific antidotes for oral FXa inhibitors, and are currently not approved for the treatment of FXa inhibitor-associated bleeding. Furthermore, the data supporting their use in this context are limited to animal and healthy volunteer studies that primarily evaluated laboratory parameters; there are no efficacy data in patients with FXa inhibitor-associated bleeding.[34,46,51,83]

Investigational Reversal Agents for FXa Inhibitors

Although no reversal agent is currently FDA-approved for FXa inhibitors, andexanet alfa and ciraparantag are being evaluatedin clinical trials.[84–86]

Andexanet Alfa—Andexanet alfa is a human recombinant FXa decoy molecule that is catalytically inactive and sequesters FXa inhibitors through high-affinity binding. Based on its mechanism of action, andexanet alfa is a potential antidote for direct and indirect FXa inhibitors. The results of multiple phase 2 studies have demonstrated the ability of andexanet alfa to reverse the anticoagulant effects of rivaroxaban, edoxaban, apixaban, enoxaparin, and betrixaban in healthy subjects.[84,87–91] Further, the ANNEXA-A and ANNEXA-R phase 3 clinical trials demonstrated the clinical efficacy of andexanet alfa in 101 healthy volunteers. In these trials, andexanet alfa rapidly reversed the anti-FXa activity of apixaban and rivaroxaban (within 2 to 5 minutes) and restored thrombin generation without serious adverse events or clinical thrombosis. Subjects who received the full dose of andexanet alfa (either as a bolus dose or a bolus plus a 2-hour infusion) had at least 80% reversal of anti-FXa activity.[85] Andexanet alfa normalized thrombin generation within 2 to 10 minutes after bolus administration in 100% of apixaban treated subjects and 96% of rivaroxaban treated subjects. Reversal of anti-FXa activity and normalization of coagulation parameters were sustained for the duration of infusion.[85]

Interim results from the ongoing phase 3b/4 ANNEXA-4 trial have further demonstrated the efficacy and safety of andexanet alfa in the reversal of FXa inhibitor activity. This study evaluated andexanet alfa in 67 patients who experienced acute major bleeding following treatment with FXa inhibitors (apixaban, rivaroxaban, or enoxaparin).[86] The administration of andexanet alfa as an intravenous bolus followed by a continuous infusion resulted in rapid

reversal of FXa inhibitor activity. Among patients evaluated for efficacy, at 12 hours post infusion, 79% had achieved hemostasis rated as excellent or good; 84% of patients with GI bleeding and 80% of patients with ICH achieved excellent or good hemostatsis.[86] At 30 days of follow-up, 18% of the patients in the safety population experienced a thromboembolic event and 15% died.[87] In this analysis, anticoagulation was restarted in 27% of patients within 30 days; however, only 1 of 12 patients with a thromboembolic event was restarted on a therapeutic dose of an anticoagulant.[86] A recent update to the ongoing ANNEXA-4 trial in 105 patients reported a 12% rate of thromboembolic events; the rate of restarting some form of anticoagulation therapy was 40%.[92]

Ciraparantag—Ciraparantag (aripazine, PER977) is an investigational reversal agent that binds several direct FXa inhibitors (apixaban, rivaroxaban, and edoxaban), the direct thrombin inhibitor dabigatran, and low molecular weight heparin. Although the mechanism of action is not well understood, ciraparantag binds to a range of anticoagulants through noncovalent hydrogen bonding and charge-charge interactions; the resulting ciraparantag/anticoagulant complex prevents the anticoagulant from binding endogenous targets and restores coagulation.[93–95] The whole blood clotting time assay is used to monitor the activity of ciraparantag in clinical trials, as the agent interferes with the assay reagents in available routine coagulation tests (ie, prothrombin test, anti-FXa assays).[93]

In a placebo-controlled phase 1/2 study, ciraparantag reversed edoxaban-induced anticoagulation in 80 healthy patients. Edoxaban administration increased the mean whole blood clotting time by a mean of 37% over patient baseline (pre-anticoagulant level). Ciraparantag was administered intravenously at doses from 100 to 300 mg, and within 30 minutes, the mean whole blood clotting time was reduced to less than 10% above baseline value. In comparison, patients treated with placebo required 12 to 15 hours for the whole blood clotting time to reach these levels. Reversal of anticoagulation was sustained for 24 hours following ciraparantag administration.[94,95]

Summary

The efficacy profiles of DOACs, including FXa inhibitors, are well established, and these treatments are associated with a number of clinical advantages. However, as with any anticoagulant, their use brings with it a risk of bleeding and increased healthcare resource utilization and costs. Also, mortality rates associated with DOAC-related major bleeding remain high, especially among patients who experience ICHs, and the lack of specific reversal agents complicates the management of bleeding among patients taking direct oral FXa inhibitors, in particular. For clinicians, including managed care stakeholders and others involved in population-based care, addressing the unmet need for a reversal agent for the management of FXa inhibitor-associated bleeding represents an opportunity to improve patient care and outcomes, as well as reduce healthcare utilization and cost.

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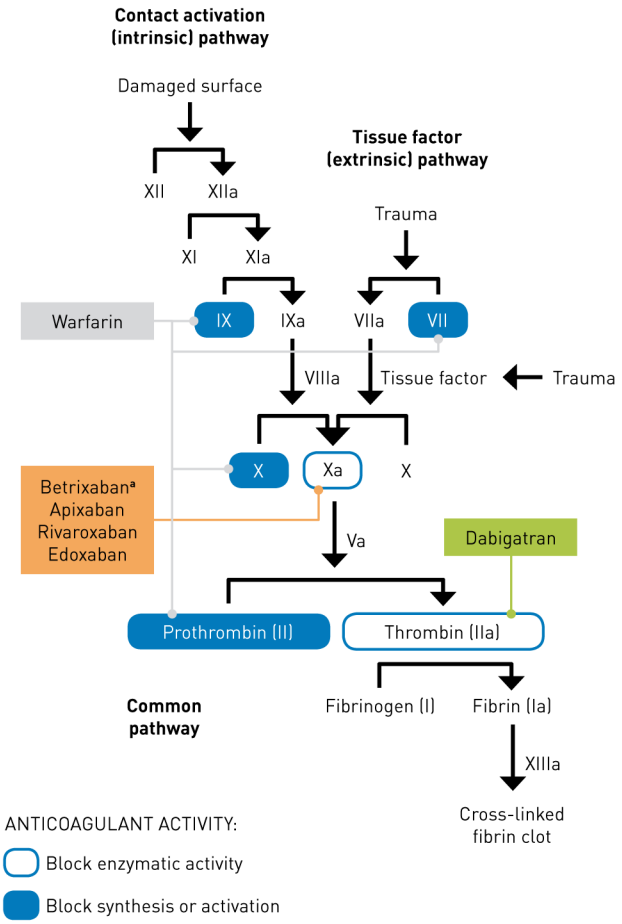

FIGURE 1.

Anticoagulation Therapy[10,21–25,43]

I indicates factor I; Ia, factor Ia; II, factor II; IIa, factor IIa; IX, factor IX; IXa, factor IXa; Va, factor Va; VII, factor VII; VIIa, factor VIIa; VIIIa, factor VIIIa; X, factor X; Xa, factor Xa; XI, factor XI; XIa, factor XIa; XII, factor XII; XIIa, factor IIa; XIIIa, factor XIIIa.

[a]Betrixaban is an investigational drug.

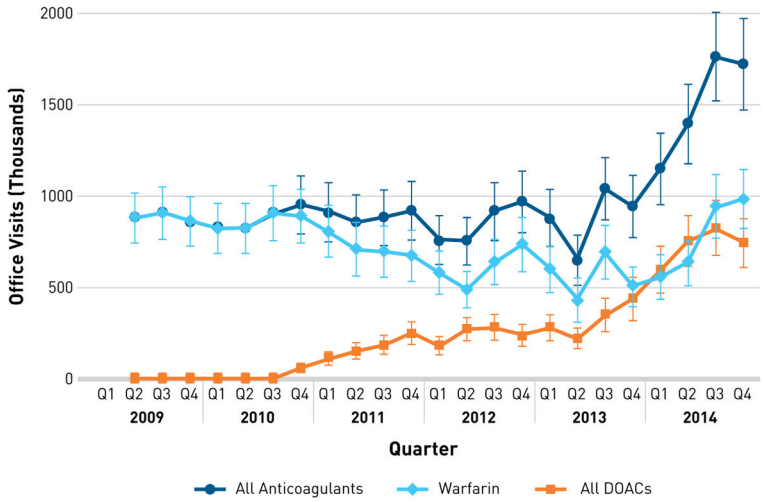

FIGURE 2.

Usage of DOACs Over Time[33]

DOAC indicates direct oral anticoagulant.

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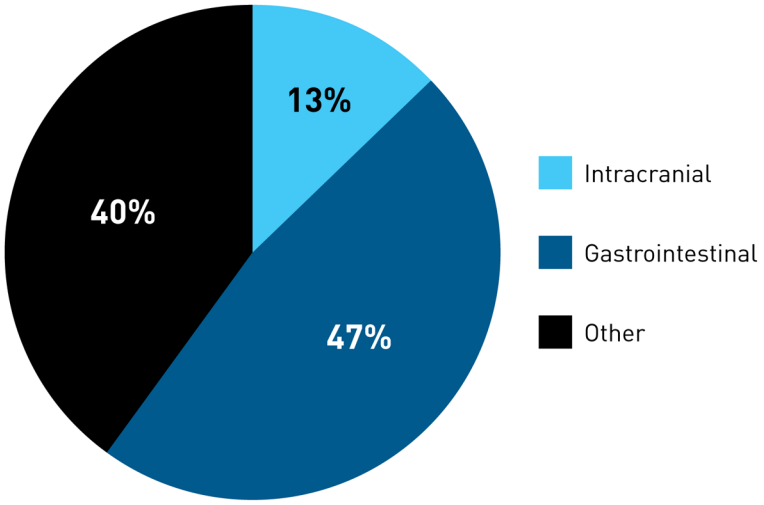
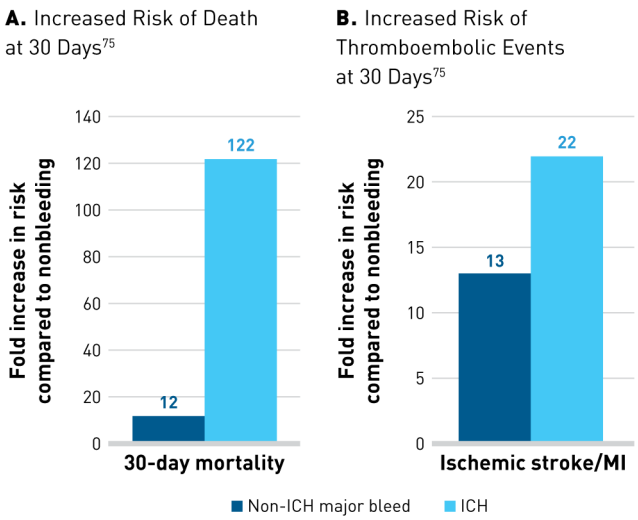


FIGURE 3.
Types of DOAC-Associated Major Bleeds[8,18,19,27,44,62–67,71]
DOAC indicates direct oral anticoagulant.



C. Rates of Thromboembolic Events After Major Bleeding[60,71,81]

Trial or Registry	Rate of Thrombo-embolic Events
ROCKET-AF (rivaroxaban)[a]	7.2%[b]
ARES registry (dabigatran, rivaroxaban, or apixaban-treated patients)	12.9% (30 days)
Dresden registry (rivaroxaban)	7.6% (35 days)

FIGURE 4.

Increased Mortality and Thromboembolic Risk After a Major Bleed[60,71,75,81]

ICH indicates intracranial hemorrhage; MI, myocardial infarction.

[a]The ROCKET AF trial was designed to compare rivaroxaban with warfarin for the prevention of stroke in patients with atrial fibrillation. Major and nonmajor clinically relevant bleeding events were evaluated as the primary safety end point.

[a]Median time to stroke or systemic embolism, 64 days (range: 16–249 days); median time to myocardial infarction/unstable angina, 282 days (range: 9–485 days).

TABLE 1

Direct Oral Anticoagulants[21–26]

Anticoagulant	Indications	FDA-Approved Reversal Agent
FXa inhibitors		
Rivaroxaban	• To reduce the risk of SSE in patients with NVAF • For the treatment of DVT and PE • For the reduction in the risk of recurrence of DVT and of PE following the initial 6 months treatment for DVT and/or PE • For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery	None
Apixaban	• To reduce the risk of SSE in patients with NVAF • For the prophylaxis of DVT, which may lead to PE in patients who have undergone hip or knee replacement surgery • For the treatment of DVT and PE • To reduce the risk of recurrent DVT and PE following initial therapy	None
Edoxaban	• To reduce the risk of SSE in patients with NVAF • For the treatment of DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant	None
Betrixaban	• Investigational agent; not yet FDA-approved. • Being investigated for extended-duration, hospital-associated prevention of VTE in acute medically ill patients.	None
Thrombin Inhibitor		
Dabigatran	• To reduce the risk of SSE in patients with NVAF • For the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5 to 10 days • To reduce the risk of recurrence of DVT and PE in patients who have been previously treated • For the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery	Idarucizumab

DVT indicates deep vein thrombosis; FXa, factor Xa; NVAF, nonvalvular atrial fibrillation; PE, pulmonary embolism; SSE, stroke or systemic embolism; VTE, venous thromboembolism.

TABLE 2

Summary of Randomized Controlled Trials of Direct Oral Anticoagulants and Risk of Hemorrhage[8,18,19,27,44,63–70,73,74]

Trial	Study Design	Patient Population	N	Primary Outcome, % Per Year[a]	Major Hemorrhage, % Per Year[a]	Intracranial Hemorrhage, % Per Year[a]
RE-LY19	RCT; dabigatran 110 or 150 mg twice daily vs warfarin[b]	Atrial fibrillation; mean $CHADS_2$ score, 2.1; aspirin use at baseline: warfarin 40.6%; dabigatran 110 mg, 40.0%; dabigatran 150 mg, 38.7%	18,113	All stroke and systemic embolism: • Warfarin, 1.69% • Dabigatran 110 mg, 1.53%[c] • Dabigatran 150 mg, 1.11%[d]	• Warfarin, 3.36% • Dabigatran 110 mg, 2.71% • Dabigatran 150 mg, 3.11%	• Warfarin, 0.74% • Dabigatran 110 mg, 0.23% • Dabigatran 150 mg, 0.30%
ROCKET-AF[18]	RCT; rivaroxaban 20 mg daily vs warfarin[b]	Atrial fibrillation; mean $CHADS_2$ score, 3.5; previous aspirin use, 40%	14,264	All stroke and systemic embolism: • Warfarin, 2.2% • Rivaroxaban, 1.70%[c]	• Warfarin, 3.40% • Rivaroxaban, 3.60%	• Warfarin, 0.70% • Rivaroxaban, 0.50%
ARISTOTLE[8]	RCT; apixaban 5 mg twice daily vs warfarin[b]	Atrial fibrillation; mean $CHADS_2$ score, 2.1; aspirin use at randomization: warfarin 30.5%, apixaban 31.3%	18,201	All stroke and systemic embolism: • Warfarin, 1.60% • Apixaban, 1.27%[d]	• Warfarin, 3.09% • Apixaban, 2.13%[d]	• Warfarin, 0.80% • Apixaban, 0.33%
ENGAGE AF TIMI 48[27]	RCT; edoxaban 60 or 30 mg daily vs warfarin[b]	Atrial fibrillation; mean $CHADS_2$ score, 2.8; concomitant aspirin, 29%	21,105	All stroke and systemic embolism: • Warfarin, 1.5% • Edoxaban 60 mg, 1.18%[c] • Edoxaban 30 mg, 1.61%[c]	• Warfarin, 3.43% • Edoxaban 60 mg, 2.75%[e] • Edoxaban 30 mg, 1.61%[e]	• Warfarin, 0.47% • Edoxaban 60 mg, 0.26%[e] • Edoxaban 30 mg, 0.16%[e]
AVERROES[73]	RCT; apixaban 5 mg twice daily vs aspirin 81–324 mg daily	Atrial fibrillation in whom VKA unsuitable (most common: patient refusal to take VKA, noncompliance with INR testing, $CHADS_2$ score of 1, serious bleeding event on VKA in 3%); mean $CHADS_2$ score of 2.0; 64% of aspirin group received 81 mg	5599	All stroke and systemic embolism: • Aspirin, 3.7% • Apixaban, 1.6%[d]	• Aspirin, 1.2% • Apixaban, 1.4%	• Aspirin, 0.4% • Apixaban, 0.4%
RE-ALIGN[74]	RCT; phase 2; dabigatran 150, 220, or 300 mg twice daily vs warfarin (INR, 2.0–3.0 or 2.5–3.5) for 12 weeks	Aortic or mitral valve replacement; primary outcome: trough dabigatran level; study terminated early for risk	252	Ischemic or unspecified stroke at 12 weeks: • Warfarin, 0% • Dabigatran, 5%	At 12 weeks: • Warfarin, 2% • Dabigatran, 4%	At 12 weeks: • Warfarin, 0% • Dabigatran, 0%

Trial	Study Design	Patient Population	N	Primary Outcome, % Per Year[a]	Major Hemorrhage, % Per Year[a]	Intracranial Hemorrhage, % Per Year[a]
EINSTEIN-DVT[44]	• RCT • Part 1: rivaroxaban 15 mg twice daily for 3 weeks then 20 mg daily vs enoxaparin SQ followed by VKA • Part 2: rivaroxaban 20 mg daily vs placebo for 6–12 months after completion of initial 6–12 months of treatment	Acute, symptomatic DVT; part 1, acute DVT; part 2, continued treatment	• Part 1, 3449 • Part 2, 1196	Recurrent VTE: • Part 1: – Enoxaparin/VKA, 3.0% – Rivaroxaban, 2.1%[c] • Part 2: – Placebo, 7.1% – Rivaroxaban, 1.3%[d]	Nonmajor bleeding: • Part 1: – Enoxaparin/VKA, 8.1% – Rivaroxaban, 8.1% Major bleeding: • Part 2: – Placebo, 0% – Rivaroxaban, 0.7%	–
EINSTEIN-PE[63]	RCT; rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg daily vs VKA	Acute symptomatic PE with or without DVT	4832	Recurrent symptomatic VTE: • VKA, 1.8% • Rivaroxaban, 2.1%[c]	• VKA, 2.2% • Rivaroxaban, 1.1%[e]	• VKA, 0.4% • Rivaroxaban, 0.1%
AMPLIFY[64]	RCT; apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months vs enoxaparin followed by warfarin[b]	Acute VTE	5395	Recurrent symptomatic VTE or death related to VTE at 6 months: • Enoxaparin/warfarin, 2.7% • Apixaban, 2.3%[c]	At 6 months: • Enoxaparin/warfarin, 1.8% • Apixaban, 0.6%[d]	At 6 months: • Enoxaparin/warfarin, 0.2% • Apixaban, 0.1%
RE-COVER I[65]	RCT; dabigatran 150 mg twice daily vs warfarin[b]	Acute VTE who initially received parenteral anticoagulation	2539	Recurrent, symptomatic, objectively confirmed VTE and related deaths at 6 months: • Warfarin, 2.1% • Dabigatran, 2.4%[c]	At 6 months: • Warfarin, 1.9% • Dabigatran, 1.6%	At 6 months: • Warfarin, 0.2% • Dabigatran, 0%
RE-COVER II[66]	RCT; dabigatran 150 mg twice daily vs warfarin[b]	Acute VTE who initially received heparin or enoxaparin	2589	Recurrent, symptomatic, objectively confirmed VTE and related deaths at 6 months: • Warfarin, 2.2% • Dabigatran, 2.3%[c]	At 6 months: • Warfarin, 1.7% • Dabigatran, 1.2%	At 6 months: • Warfarin, 0.2% • Dabigatran, 0.2%
Hokusai-VTE[67]	RCT; edoxaban 60 mg daily (30 mg daily in patients with renal insufficiency) vs warfarin[b]	Acute VTE who initially received heparin	8240	Recurrent symptomatic VTE: • Warfarin, 3.5% • Edoxaban, 3.2%[c]	• Warfarin, 1.6% • Edoxaban, 1.4%	• Warfarin, 0.4% • Edoxaban, 0.1%

Trial	Study Design	Patient Population	N	Primary Outcome, % Per Year[a]	Major Hemorrhage, % Per Year[a]	Intracranial Hemorrhage, % Per Year[a]
ADOPT[68]	RCT; oral apixaban 2.5 mg twice daily for 30 days vs SQ enoxaparin 40 mg daily for 6 to 14 days	Acutely ill patients with at least 1 additional risk factor for VTE and hospitalized with an expected stay of at least 3 days	6528	30-day total VTE event or VTE-related death: • Enoxaparin, 3.06% • Apixaban, 2.71%	• Enoxaparin, 0.19% • Apixaban, 0.47%	• Enoxaparin, 0.06% • Apixaban, 0%
MAGELLAN[69]	RCT; SQ 40 mg enoxaparin once daily for 10 ± 4 days and oral placebo for 35 ± 4 days vs SQ placebo 10 ± 4 days and oral rivaroxaban 10 mg once daily for 35 ± 4 days	Acutely ill patients at least 40 years of age, hospitalized for less than 72 hours and with reduced mobility	8101	VTE event or VTE-related death at day 10 and day 35 At day 10: • Rivaroxaban, 2.7% • Enoxaparin, 2.7% At day 35: • Extended-duration rivaroxaban, 4.4% • Extended-duration enoxaparin-placebo, 5.7%	At day 10: Rivaroxaban, 0.6% Enoxaparin, 0.3% At day 35: • Extended-duration rivaroxaban, 1.1% • Extended-duration enoxaparin-placebo, 0.4%	–
APEX[70]	RCT; SQ enoxaparin 40 mg once daily for 10 ± 4 days and oral betrixaban placebo for 35–42 days vs SQ enoxaparin placebo for 10 ± 4 days and oral betrixaban 80 mg once daily for 35–42 days	Acutely ill patients at least 40 years of age, hospitalized for less than 96 hours and with reduced mobility, at risk for VTE	7513	VTE-related death, nonfatal PE, asymptomatic proximal DVT, or symptomatic DVT between days 32 and 47: • Enoxaparin 7.0% • Betrixaban 5.3%	• Enoxaparin, 0.6% • Betrixaban, 0.7%	• Enoxaparin, 0.19% • Betrixaban, 0.05%

CHADS2 indicates congestive heart failure, hypertension, age, diabetes, stroke (doubled); DVT, deep vein thrombosis; INR, international normalized ratio; PE, pulmonary embolism; RCT, randomized controlled trial; SQ, subcutaneous; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a] Unless otherwise specified.

[b] The target INR was 2.0–3.0 for the warfarin group in each study (unless otherwise noted).

[c] Statistically significant for noninferiority.

[d] Statistically significant for superiority.

[e] Statistically significant.